

Claims.

1. The use of at least one active substance for the prophylaxis and/or therapy of at least one viral disease, characterized by that the active substance inhibits a cellular caspase such that a virus multiplication is inhibited.

5 2. The use of at least one active substance according to claim 1, characterized by that the caspase is the caspase-3.

10 3. The use of at least one active substance according to one of claims 1 to 2, characterized by that the active substance(s) is (are) selected from the following active substances:

15 - peptide and non-peptide inhibitors of the cellular caspase-3, such as

- Z-DEVD-FMK (Alexis Biochemicals)
- Ac-DEVD-CHO (Alexis Biochemicals)
- Ac-DMQD-CHO (Alexis Biochemicals)
- Z-D(OMe)E(OMe)VD(OMe)-FMK (Alexis Biochemicals)
- 20 • Z-D(OMe)QMD(OMe)-FMK (Alexis Biochemicals),

- inhibitors of cellular caspases, which can activate caspase-3, such as

- 25 • peptide and non-peptide inhibitors of the caspase-9, such as
  - Z-LE(OMe)HD(OMe)-FMK (Alexis Biochemicals)
  - Z-LEHD-FMK (Alexis Biochemicals)
  - Ac-LEHD-CHO (Alexis Biochemicals),

- peptide and non-peptide inhibitors of the caspase-8, such as
  - Z-LE(OMe)TD(OMe)-FMK (Alexis Biochemicals)
  - Ac-ESMD-CHO (Alexis Biochemicals)
  - Ac-IETD-CHO (Alexis Biochemicals)
  - Z-IETD-FMK (Alexis Biochemicals),
- peptide and non-peptide inhibitors of the caspase-10, such as
  - Ac-AEVD-CHO (Alexis Biochemicals)
  - Z-AEVD-FMK (Alexis Biochemicals),
- peptide and non-peptide inhibitors of other caspases or granzyme B and pan-caspase inhibitors, such as
  - Z-VAD-FMK (Alexis Biochemicals)
  - Z-VAD-(OMe)-FMK (Alexis Biochemicals)
  - Ac-YVAD-CHO (Calbiochem)
  - Z-YVAD-FMK (Calbiochem)
  - Z-VDVAD-FMK (Calbiochem)
  - Ac-LEVD-CHO (Calbiochem),

- an inhibitory peptide, in particular Z-VAD-FMK or Z-DEVD-FMK,

- an non-peptide inhibitor of caspases,

- dominant-negative mutant of a caspase,

- an antisense-oligonucleotide, which specifically accumulates at the DNA sequence or mRNA sequence coding for a cellular caspase and inhibit the transcription or translation thereof,

- a protein, which inhibitingly acts on caspases, for instance the cellular inhibitors of

apoptosis proteins cIAP1, cIAP2, the X-linked inhibitor of apoptosis protein XIAP, the antiapoptotic protein Bcl-2 or the baculoviral protein p35,

5 - dsRNA oligonucleotides, which are suitable for the specific degradation of the mRNA's of a cellular caspase by the RNAi technology,

10 - an antibody or antibody fragment specific for a caspase or a fusion protein containing at least one antibody fragment, for instance a Fv fragment, which inhibits the protease activity of a caspase.

15 4. The use of at least one active substance according to one of claims 1 to 4, characterized by that the viral disease is caused by RNA or DNA viruses, preferably influenza viruses.

20 5. A combination preparation for the prophylaxis and/or therapy of at least one viral disease, comprising at least two antiviral active substances, wherein at least one antiviral active substance is selected from the active substances according to claim 3, wherein the combination preparation can be used in the form of a mixture or as individual components for using them simultaneously or at different times at identical or different places.

25 6. A combination preparation for the prophylaxis and/or therapy of a viral disease, com-

prising at least one active substance according to one of claims 1 to 5 and at least one antivirally acting substance, which is a kinase inhibitor.

5       7. A combination preparation for the prophylaxis and/or therapy of a viral disease, comprising at least one active substance according to one of claims 1 to 5 and at least one antivirally acting substance, which is a 1-adamantanamine, a rimantadine, a neuraminidase inhibitor or a nucleoside analog such as ribavirin.

10       8. An active substance or a combination preparation according to one of claims 1 to 7 for the prophylaxis and/or therapy of an infection with negative-strand RNA viruses, in particular influenza viruses or Borna viruses.

15       9. A test system for finding active substances, which act on at least one cellular caspase, in particular caspase-3, such that a virus multiplication is inhibited, comprising

20       a. at least one cell infectable with at least one virus and comprising at least one cellular caspase and at least one virus infecting the cells, or

25       b. at least one cell infectable with at least one virus and comprising at least one cellular caspase.

10. A test system according to claim 9, characterized by that the virus is an RNA or DNA virus, preferably an influenza virus.

5 11. A test system according to claim 9 or 10, characterized by that the cell comprises at least one overexpressed caspase, in particular caspase-3.

10 12. A test system according to one of claims 9 to 11, characterized by that it comprises a cell, in which at least one gene coding for at least one dominant-negative mutant of at least one caspase is expressed.

15 13. A test system according to one of claims 9 to 12, characterized by that it comprises a cell, in which the expression for at least one caspase, in particular caspase-3, is inhibited.

20 14. A method for identifying at least one active substance for the prophylaxis and/or therapy of viral diseases, which substantially inhibits or inhibit the multiplication of viruses during viral diseases, comprising the following steps:

25 a. bringing at least one test system according to one of claims 9 to 14 into contact with at least one potential active substance, and

b. determining the effects on the virus multiplication.

5 15. A method for preparing a drug for the prophylaxis and/or therapy of a viral disease, which substantially inhibits the multiplication of viruses during viral diseases, comprising the following steps:

10 a. performing a test system according to one of claims 9 to 15, and

b. reacting the active substance(s) with at least one auxiliary and/or additional substance.

15 16. The use of at least one caspase inhibitor, in particular a caspase-3 inhibitor, for preparing a pharmaceutical composition for the prophylaxis and/or therapy of a viral infection, in particular an infection with an RNA negative-strand virus, preferably an influenza infection.

20 17. The use according to claim 16, wherein the pharmaceutical composition in addition comprises at least one further antiviral active substance, which is not a caspase inhibitor, in particular an inhibitor of one or several cellular kinases.

25 18. A combination preparation, in particular for the treatment of a viral infection, comprising at least one caspase inhibitor and another

5 antiviral active substance, which is not a caspase inhibitor, in particular an inhibitor of one or several cellular kinases, each in a physiologically well tolerated dose, and galenic auxiliary and carrier substances, wherein the caspase inhibitor and the further antiviral active substance may exist in a mixture or in separate galenic preparations, intended for the simultaneous or successive administration.

10 19. The use or a combination preparation according to one of claims 16 to 18, wherein the caspase inhibitor is selected from the group consisting of the substances according to claim 3 and mixtures of such substances.

15 20. The use or a combination preparation according to one of claims 16 to 19, wherein the further antiviral active substance is selected from the group consisting of "neuraminidase inhibitors, nucleoside analogs, 1-adamantanamine, 20 rimantadine, ribavirin, Relenza, 3-deazaadenosine, MEK inhibitors, in particular from the substance groups butadiene derivatives, flavon derivatives and benzamide derivatives, 2-(2-amino-3-methoxyphenyl)-4-oxo-4H-(1)benzopyran, U0126, PD18453, PD98059, inhibitors of a kinase 25 of the NF- $\kappa$ B signal transduction pathway, e.g. non-steroidal anti-inflammatory substances inhibiting the NF- $\kappa$ B activity, such as phenyl alkyl acid derivatives such as sulindac or derivatives of sulindac such as sulindac sulphoxide, sulindac sulphone, sulindac sulphide, benzylamide sulindac analogs, salicylic acid deriva- 30

tives, such as salicylic acid or acetosalicyl acid, salicylamide, salacetamide, ethenzamide, diflunisal, olsalazine or salazosulphapyridine, curcumin, antioxidants such as pyrrolidine dithiocarbamate (PDTC), oxicams, such as piroxicam, vitamin E and derivatives thereof, such as pentamethyl hydroxychromane (PMC), 17 beta-oestradiol and derivatives thereof, polyphenoles of the tea such as 5 Epigallocatechin-3-gallate (EGCG), Bay11-7182, peptides, which inhibit the interaction of at least two components of the NF-kB signal transduction pathway, for instance peptides binding to NEMO, proteosome inhibitors, such as 10 PS-341 and lactacystin, antisense-oligonucleotides, which specifically accumulate at the DNA sequence or m-RNA sequence coding for a component of the NF-kB signal transduction pathway and inhibit the transcription or 15 translation thereof, for instance antisense-nucleotide sequences specific for p65 or p50, dominant-negative mutants of a component of the NF-kB signal transduction pathway, dsoligonucleotides, which are suitable for the 20 specific degradation of the mRNA's of a component of the NF-kB signal transduction pathway by the RNAi technology, antibodies and antibody fragments specific for a component of the NF-kB signal transduction pathway, or fusion 25 proteins containing at least one antibody fragment, for instance a Fv fragment, which inhibit at least one component of the NF-kB signal transduction pathway, kinase-inhibiting flavon derivative or benzpyran derivative; kinase-inhibiting derivative of the 4H-1-benzopyran; 30 flavopiridol derivative; 2-(2-amino-3-methoxy- 35

phenyl)-4-oxo-4H-(1)benzopyran; 7,12-dihydro-indolo (3,2-d) (1)benzazepin-6(5H)-on; 70H-staurosporine and/or a phosphokinase-inhibiting derivative of the 70H-staurosporine; butyrolactone; roscovitine; purvalanol A; emodin; anilinoquinazoline; phenylaminopyrimidine; trioylimidazole; paullone; [4-(4-fluorophenyl)-2-(4-methylsulfinylphenyl)-5-(4-pyridyl)1H-imidazole; [1,4-diamino-2,3-dicyano-1,4-  
10 bis(2aminophenylthio) butadiene; kinase-inhibiting derivative of the butadiene; [2-2'-amino-3'-methoxyphenyl)-oxa-naphthalen-4-on); [2-(2-chloro-4-iodo-phenylamino)-N-cyclo-propylmethoxy-3,4-difluoro benzamide; CEP-1347 (KT7515)  
15 bis-ethylthiomethyl; tetrapyrrolic macrocycles; pyrimidone derivative; 3-aminomethylen-indoline derivative; pyrazolo (3,4-b) pyridine derivative; pyrazole derivative; 1,4-substituted piperidine derivative; lipoidic ammonium salt; dominant-negative mutant of a kinase of a cellular signal transduction pathway; antisense-oligonucleotide, which specifically accumulates at the DNA sequence or mRNA sequence coding for a kinase of a cellular signal transduction pathway  
20 and inhibits the transcription or translation thereof; dsoligonucleotides, which are suitable for degradation of the mRNA's from kinases of a cellular signal transduction pathway by the RNAi technology; antibodies and antibody fragments specific for a kinase or a fusion protein containing at least one antibody fragment, for instance a Fv fragment, which inhibits the kinase activity of a kinase module; and/or a peptide, which inhibits the interaction of at  
25 least two kinases preferably activatable immediately after one another of a cellular

signal transduction pathway, and mixtures of such substances".

5           21. A method for screening for prospective antiviral active substances, comprising the following steps:

- a) a cell containing a caspase, in particular caspase-3, is infected with a virus, in particular an RNA negative-strand virus, preferably an influenza virus,
- 10           b) the cell is contacted with one or several prospective active substances,
- c) the viral replication in the cell is determined,
- 15           d) an active substance or a mixture of active substances is selected, if the viral replication measured in step c) is smaller than when executing steps a) to c), however without a prospective active substance or with an inactive active substance,
- 20           e) as an option, a selected active substance is contacted with a cell infected with a virus, which does not express or contain a caspase, in particular caspase-3, and the viral replication is measured, and the active substance is further selected, if the measurement of the viral replication does not result in a significant modification relative to a measurement when contacting said infected cell with an inactive active substance or without any active substance,

wherein the steps a) and b) may occur in any order or simultaneously, and wherein the steps a) to d) on the one hand and the step e) on the other hand may occur in any order or simultaneously.